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Marshall-Stickler Phenotype Associated With von Willebrand Disease

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We report on 6 individuals from three different kindreds with Marshall-Stickler (MS) phenotype, with characteristic orofacial abnormalities, arthropathy, deafness, and eye findings, all of whom were discovered to have a mild bleeding diathesis and coagulation-study findings consistent with mild von Willebrand disease (vWD). MS syndrome has been linked in some cases to the type II procollagen gene (COL2A1) on chromosome 12q, and to the collagen XI gene (COL11A2) on chromosome 6. The von Willebrand factor (vWF) is encoded by a 180-Kb gene located on the short arm of chromosome 12. This is the first reported association of these two disorders. Am. J. Med. Genet. 68:121–126, 1997 © 1997 Wiley-Liss, Inc.

KEY WORDS: Marshall-Stickler syndrome; von Willebrand disease; chromosome 12; coagulopathy; bleeding diathesis; platelet aggregation

INTRODUCTION

Marshall-Stickler syndrome (MS) is an autosomal-dominant connective tissue disorder characterized by ocular and orofacial abnormalities, arthropathy, and deafness. Prevalence is estimated at 1:10,000 people [Pyeritz, 1989]. Eye findings include severe myopia, myopic degeneration of the retina, retinal detachments, vitreoretinal degeneration, astigmatism, cataracts, strabismus, and glaucoma. Orafacial findings include midface hypoplasia with malar flattening, micrognathia, Pierre Robin sequence, and abnormal palatal mobility. Patients may have short stature or a marfanoid body habitus, with enlarged, often hyperextensible joints and early arthritis. Radiographic findings resemble a mild spondyloepiphyseal dysplasia. Deafness can be severe and progressive. It is generally sensorineural, but may have a conductive component. There is considerable intra- and interfamilial variability [Temple, 1989; Vintiner et al., 1991]. This variability has caused controversy as to whether MS represents a single genetic entity, along with Wagner and Weissenbacher-Zweymüller syndromes. Wagner syndrome is an autosomal-dominant vitreoretinal degeneration. Weissenbacher-Zweymüller syndrome is thought to be the neonatal presentation of Stickler syndrome with characteristic X-ray findings which later regress [Temple, 1989]. Stickler syndrome has been linked to the gene for type II procollagen (COL2A1) on chromosome 12(q13.11–13.2) in many families [Francomano et al., 1987]. It has been speculated that clinical heterogeneity may be the effect of different alleles at the same locus [Temple, 1989], or of several different gene loci in families unlinked to COL2A1 [Knowlton et al., 1989; Fryer et al., 1990, Zlotogora et al., 1992], or it may be a function of the location and nature of the mutation found at COL2A1 [Körkkö et al., 1993]. There have been 4 cases of mutations causing premature termination codons in the COL2A1 gene in patients with MS [Ahmad et al., 1991, 1993; Brown et al., 1992; Ritvaniemi et al., 1993]. More recently, MS linkage has been demonstrated to the (COL11A2) locus on the short arm of chromosome 6 [Brunner et al., 1994], and a splice donor site mutation resulting in in-frame exon skipping has been found in patients with MS [Vikkula et al., 1995].

Von Willebrand disease (vWD) is a common autosomal-dominant bleeding disorder affecting up to 1.3% of the population [Werner et al., 1993]. Penetrance and expression are variable; it is usually associated with mild-to-moderate mucosal bleeding, but patients may range from asymptomatic to severely affected within the same family. Patients typically report epistaxis, menorrhagia, gastrointestinal bleeding, and excessive bruising and bleeding with surgical procedures or mild mouth trauma with dental procedures. The von Willebrand factor (vWF) is a large protein, synthesized in vascular endothelial cells and megakaryocytes, and it normally exists as a series of multimeric forms of varying sizes in plasma. Biosynthesis includes dimerization and polymerization of vWF and proteolytic cleavage of a propeptide to form a series of multimers of varying sizes. A number of distinct types and subtypes of vWD have been characterized based on laboratory findings and variability in degree of clinical symptoms [Ginsburg, 1992]. The ABO blood group modifies vWF,

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with type O individuals having the lowest levels of vWF [Gill et al., 1987].

Type I is the most common variant, seen in approximately 70% of patients with vWD [Ginsburg, 1992]. Patients have a prolonged bleeding time, mild-to-moderate decrease in vWF antigen, and vWF activity (also known as factor VIII: ristocetin cofactor) with normal distribution of vWF multimers. They also have in vivo absent platelet aggregation with low doses of the antibiotic, ristocetin. Patients with type II vWD have an abnormal size distribution of vWF multimers and low-to-normal amounts of vWF antigen and activity. The type II subtypes are characterized by differences in multimeric pattern. Type III vWD patients show a marked decrease or absence of vWF activity and antigen, and have more severe bleeding. Treatment depends on vWD subtype. Desmopressin (DDAVP) is the treatment of choice for type I vWD and normalizes the coagulation functions. It is usually ineffective in types II and III and is contraindicated in patients with type IIb [Ginsburg, 1992]. The vWF gene has been cloned, and it is located on the short arm of chromosome 12 (p12–pter) [Ginsburg et al., 1985; Mancuso et al., 1989]. No single distinct genetic defect has been found for classic type I vWD [Ginsburg and Sadler, 1993].

CLINICAL REPORTS

Patient 1

R.R. (Fig. 1) is a 23-year-old woman who was ascertained during preconceptual counseling due to her use of Dilantin® for a partial complex seizure disorder. She had a long-standing diagnosis of vWD. Other problems include left sensorineural hearing loss, severe myopia first noted at age 1 year, scoliosis, and joint problems of the knees and ankles. She has a history of peptic ulcer and kidney infections, sebaceous cysts, and a birthmark on her leg. She complains of menorrhagia, and had excessive bleeding after a skin biopsy. Her mother has vWD, myopia, arthropathy with early adulthood onset, and retinal detachment. Other maternal relatives are also reported to have joint problems.

Physical examination showed a relatively flat face with malar hypoplasia, hyperextensible joints and marked flat feet, and a slightly hyperpigmented macule with irregular borders on the right thigh. Results of coagulation studies (Table I) were consistent with mild type I vWD.

Patients 2–4

T.S. (Fig. 2) and J.A. (Fig. 3) are half-sisters ages 22 and 17 years, respectively. They and their mother, S.M.

Fig. 1. Frontal (**a**) and lateral (**b**) views of patient 1.

TABLE I. Coagulation Studies*

Test	R.R.	S.M.	T.S.	J.A.	D.E.J.	D.A.J.
Bleeding time	↑	Normal	↑	↑	↑	↑
PT	Normal	Normal	Normal	Normal	Normal	Normal
PTT	Normal	Normal	Normal	Normal	Normal	Normal
vWF activity	Low normal	Low normal	Normal	Low	Low normal	Normal
vWF antigen	Low normal	Low normal	Low normal	Low	Low normal	Normal
Factor VIII	Low normal	Low	Normal	Low	Normal	Normal
Multimers	Normal	Normal	Normal	Normal	Not done	Normal
RIPA-LD	Absent	Not done	Absent	Absent	Absent	Absent
Response to DDAVP	Good	Good	Not done	Not done	Good	Good
Blood type	O+		Not done	O+	O+	A−
vWD type	I	I	I	I	I	I

*PT, protime; PTT, partial thromboplastin time; RIPA-LD, ristocetin-induced platelet aggregation to low-dose ristocetin; ↑, increased.

(Fig. 3), age 43, have a history of joint hypermobility, similar facial appearance, and bleeding problems. T.S. also has a history of cleft palate, moderate mental retardation, and seizure disorder. She was the product of a traumatic forceps delivery with skull fracture, and had antenatal central nervous system bleeding and seizures. She also has severe myopia (−10 diopters), right exotropia, and mild bilateral sensorineural hearing loss. J.A. and S.M. are of normal intellect, and have normal hearing. S.M. has severe myopia, history of glaucoma, and retinal tear; J.A. has normal vision. These patients have a history of epistaxis, menorrhagia, and excessive bleeding, postoperatively for T.S., and after palate repair and with childbirth for S.M. J.A. received cryoprecipitate prophylactically before childbirth. All report hyperextensible joints of hands, wrists, and hips. S.M. has had a history of osteoarthritis since age 33. They deny heart murmurs or cardiac problems. Two maternal uncles are said to have bleeding problems. Another full sibling of T.S., S.S., had similar

Fig. 2. Frontal (**a**) and lateral (**b**) views of patient 2.

Fig. 3. Patients 4, 3, and 2, beginning at left.

bleeding problems, joint symptoms, and laboratory findings, but died several years ago in an automobile accident.

On exam, height was <5th centile for T.S., 5th centile for S.M., and 25th centile for J.A., with weight at 75–90% for all. All had some degree of malar flattness and retrognathia. They can touch their tongues to their noses. S.M. has prominent scars; T.S. and J.A. do not, and their skin is not hyperextensible, velvety, or translucent. All have slender, tapering fingers, with increased joint mobility at fingers and wrists and hyperextensibility at the elbows. S.M. and T.S. reported hip hyperextensibility when younger. S.M., T.S., J.A., and S.S. have had similar coagulation profiles with prolonged bleeding times, low-to-low-normal factor VIII levels, and decreased ristocetin-induced platelet aggregation. S.M. has not had platelet aggregation studies due to financial constraints.

Patients 5 and 6

D.A.J. (Fig. 4) and D.E.J. (Fig. 5) are brother and sister, respectively. They were both born with a cleft of the soft palate. Their retromicrognathia was severe enough to require tracheostomy during infancy in both. The older sib, D.E.J., has right sensorineural and left, primarily conductive, hearing loss, and hyperextensible joints. D.A.J. has a right sensorineural and left mixed hearing loss, and had bilateral hydrocele repair. Intelligence is normal in both. They both have had bleeding problems with surgery, and were subsequently diagnosed with vWD. Family history is remarkable for their mother having a small lower jaw at birth, hyperextensible joints, flat feet, arthritis, strabismus, and

Fig. 4. Frontal (**a**) and lateral (**b**) views of patient 5, age 18 years.

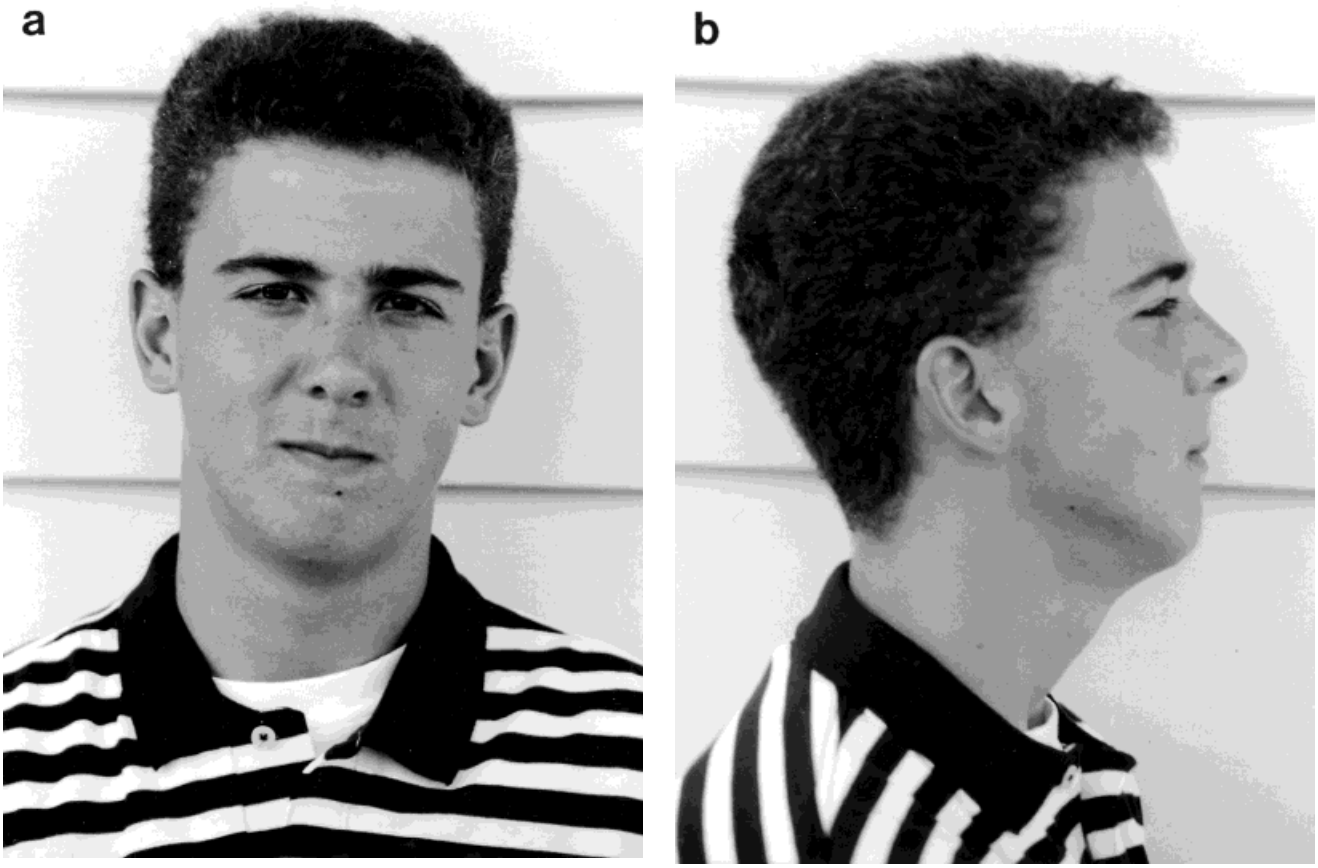

Fig. 5. Frontal (**a**) and lateral (**b**) views of patient 6, age 16 years.

cataracts, as well as for other maternal relatives with joint problems and myopia. Their father has a high-arched palate and a speech defect attributed to his sensorineural hearing loss. Both paternal and maternal grandmothers had early arthritis and nerve deafness, and other family members had myopia, cataracts, hearing loss, and arthropathy. The father was told "he was a bleeder" as a child, but reports no clinically significant bleeding problems anymore and has not had formal evaluation. The diagnosis of vWD was made after D.E.J. had perioperative bleeding problems with cleft-palate repair, leading to coagulation evaluation of both sibs.

Both D.A.J. and D.E.J. have less severe micrognathia and facial flattening than noted in infancy, but both still have marked malar hypoplasia, and normal stature when last evaluated at ages 14 and 15 years. They have no ophthalmologic abnormalities. Both sibs and their parents had normal karyotypes on prometaphase chromosome preparations. Coagulation studies (Table I) on both sibs were consistent with mild type I vWD.

DISCUSSION

Marshall-Stickler syndrome and von Willebrand disease are autosomal-dominant disorders known for their variable expressivity. Von Willebrand disease is the most common inherited bleeding disorder; although the incidence of MS is much lower than that of vWD, it is not rare. Both may be underdiagnosed in less severely affected individuals [Temple, 1989; Werner et al., 1993].

There are no other reports in the literature of patients with both of these disorders. Mitral valve prolapse, which is found in 45% of patients with MS [Lieberfarb et al., 1986], has been reported to occur in 6 patients with vWD in three case reports [Chevallier et al., 1989; Diez-Ewald et al., 1991; Uniskiewicz and Kuczewska-Stanecka, 1992]. Review of the literature did not document other reports of major anomalies of MS with those of vWD. Both MS and vWD have been mapped to genes on chromosome 12: MS to COL2A1 on the q arm, and vWD to vWF on the p arm. Prometaphase chromosomes were done on 3 of our 6 patients and showed no translocations to account for the coexistence of these disorders. If these patients have abnormalities in procollagen, one might speculate that it results in an altered collagen-vWF binding at the platelet glycoprotein lb domain or at the other possible collagen-binding domain between amino acids 911–1365. However, the decreased ristocetin-induced platelet aggregation seen in our patients is consistent with mild type I vWD and occurs in vitro due to an interaction proposed to be between the platelet glycoprotein lb receptor of vWF and ristocetin [Azuma et al., 1993]. This suggests a defect in vWF and vWF-platelet aggregation in these patients.

We found this association of vWD and MS, in 6 of 51 MS patients followed at our center, intriguing. The lack of chromosome 12 rearrangement in 3 patients who had karyotypes done was initially surprising. However, the growing evidence for genetic heterogeneity in MS makes this less so. A contiguous gene mutation at an alternative locus for MS and/or vWD could be involved. The considerable posttranslation processing required for both vWF and collagen may indicate another explanation. Perhaps a single-gene mutation alters the processing of both proteins.

Regardless of the cause, there could be some important considerations for patients with MS and vWD. Many MS patients have surgery, especially for cleft-palate repair. It would be prudent to elicit history of mild bleeding and bruising symptoms, and to consider obtaining a preoperative bleeding time. Conversely, unless an in-depth family history of MS-associated symptoms were specifically sought, this diagnosis could go undetected in patients with vWD.

Further history and evaluations by physicians dealing with both populations of patients will help to clarify the prevalence and etiology of this coexistence of disorders, and will be of benefit to both MS and vWD patients.

REFERENCES

Ahmad NN, Ala-Kokko L, Knowlton RG, Jimenez SA, Weaver EJ, Maguire JI, Tasman W, Prockop DJ (1991): Stop codon in the procollagen II gene (COL2A1) in a family with the Stickler syndrome (arthro-ophthalmopathy). Proc Natl Acad Sci USA 88: 6624–6627.

Ahmad NN, McDonald-McGinn DM, Zackai EH, Knowlton RG, LaRossa D, DiMascio J, Prockop DJ (1993): A second mutation in the type II procollagen gene (COL2A1) causing Stickler syndrome (arthro-ophthalmopathy) is also a premature termination codon. Am J Hum Genet 52:39–45.

Azuma H, Sugimoto M, Ruggeri Z, Ware J (1993): A role for von Willebrand factor proline residues 702–704 in ristocetin-mediated binding to platelet glycoprotein 1b. Thromb Haemost 69:192–196.

Brown DM, Nichols BE, Weingeist TA, Sheffield VC, Kimura AE, Stone EM (1992): Procollagen II gene mutation in Stickler syndrome. Arch Ophthalmol 110:1589–1593.

Brunner HG, van Beersum SE, Warman ML, Olsen BR, Ropers HH, Mariman EC (1994): A Stickler syndrome gene is linked to chromosome 6 near the COL11A2 gene. Hum Mol Genet 3:1561–1564.

Chevallier B, Bidat E, Aurousseau MH, Gaudelus J, Perelman R (1989): Mitral valve prolapse and Willebrand disease. Study of 16 cases of Willebrand disease. Ann Pediatr (Paris) 36:435–438.

Diez-Ewald M, Vizcaino G, Arteaga-Vizcaino M, Fernandez N, Weir-Medina J, Gomez O (1991): Epidemiology of von Willebrand's disease in the state of Zulia, Venezuela. Invest Clin 32:187–199.

Francomano CA, Lieberfarb RM, Hirose T, Maumenee IH, Streeten EA, Meyers DA, Pyeritz RE (1987): The Stickler syndrome: Evidence for close linkage to the structural gene for type II collagen. Genomics 1:293–296.

Fryer AE, Upadhyaya M, Littler M, Bacon P, Watkins D, Tsipouras P, Harper PS (1990): Exclusion of COL2A1 as a candidate gene in a family with Wagner-Stickler syndrome. J Med Genet 27: 91–93.

Gill JC, Endres-Brooks J, Bauer PJ, Marks WJ Jr, Montgomery RR (1987): The effect of ABO blood group on the diagnosis of von Willebrand disease. Blood 79:1691–1695.

Ginsburg D (1992): Biology of inherited coagulopathies: Von Willebrand factor. Hematol Oncol Clin North Am 6:1011–1020.

Ginsburg D, Sadler JE (1993): Von Willebrand disease: A database of point mutations, insertions, and deletions. For the Consortium on von Willebrand Factor Mutations and Polymorphisms, and the Subcommittee on von Willebrand Factor of the Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis. Thromb Haemost 69:177–184.

Ginsburg D, Handin RI, Bonthron DT, Donlon TA, Bruns GAP, Latt SA, Orkin SH (1985): Human von Willebrand factor (vWF): Isolation of complementary DNA (CDNA) clones and chromosomal localization. Science 228:1401–1406.

Kida S (1990): Studies on von Willebrand factor antigen in endothelial cells and sera of patients with connective tissue diseases. Ryumachi 30:17–25.

Körkkö J, Ritvaniemi P, Haataja L, Kääriäinen H, Kivirikko KI, Prockop DJ, Ala-Kokko L (1993): Mutation in type II procollagen (COL2A1) that substitutes asparate for glycine alpha 1-67 and that causes cataracts and retinal detachment: Evidence for molecular heterogeneity in the Wagner syndrome and the Stickler syndrome (arthro-ophthalmopathy). Am J Hum Genet 53:55–61.

Knowlton RG, Weaver EJ, Struyk AF, Knobloch WH, King RA, Norris K, Shamban A, Uitto J, Jimenez SA, Prockop DJ (1989): Genetic linkage analysis of hereditary arthro-ophthalmopathy (Stickler syndrome) and the type II procollagen gene. Am J Hum Genet 45:681–688.

Lieberfarb RM, Goldblatt A (1986): Prevalence of mitral valve prolapse in the Stickler syndrome. Am J Med Genet 24:387–392.

Mancuso DJ, Tuley EA, Westfield LA, Worrall NK, Shelton-Inloes BB, Sorace JM, Alevy YG, Sadler JE (1989): Structure of the gene for human von Willebrand factor. J Biol Chem 264:19514–19527.

Pyeritz RE (1989): Heritable and developmental disorders of connective tissue and bone. In McCarty DJ (ed): "Arthritis and Allied Conditions: A Textbook of Rheumatology." Philadelphia: Lea & Febiger, pp 1332–1359.

Ritvaniemi P, Hyland J, Ignatius J, Kivivikko KI, Prockop DJ, Ala-Kokko L (1993): A fourth example suggests that premature termination codons in the COL2A1 gene are a common cause of the Stickler syndrome: Analysis of the COL2A1 gene by denaturing gradient gel electrophoresis. Genomics 17:218–221.

Temple IK (1989): Stickler's syndrome. J Med Genet 26:119–126.

Uniskiewicz B, Kuczewska-Stanecka K (1992): Coexistence of von Willebrand's disease with mitral valve prolapse. Pol Tyg Lek 47: 927–929.

Vikkula M, Mariman EC, Lui VC, Zhidkiva NI, Tiller GE, Goldring MB, van-Beersum SE, de Waal Malefijt MC, van den Hoogen FH, Ropers HH, et al. (1995): Autosomal dominant and recessive osteochondrodysplasias associated with the COL11A2 locus. Cell 80:431–437.

Vintiner GM, Temple IK, Middleton-Price HR, Baraister M, Malcom S (1991): Genetic and clinical heterogeneity of Stickler syndrome. Am J Med Genet 41:44–48.

Werner EJ, Broxson EH, Tucker EL, Giroun DS, Shults J, Abshire TC (1993): Prevalence of von Willebrand disease in children: A multiethnic study. J Pediatr 123:893–898.

Zlotogora J, Sagi M, Schuper A, Leiba H, Merin S (1992): Variability of Stickler syndrome. Am J Med Genet 42:337–339.